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10/776,669	02/11/2004	Alvin C. Powers	VBLT:033US	3480

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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,669	POWERS ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 2/11/2004 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/21/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-30 are under consideration.

Drawings

2. The drawings are objected to under 37 CFR 1.83(a) because they fail to show the details as described in the specification. For example, figure numbers 1-5 and 10 do not show any structural detail as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are

not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

3. Claim 29 objected to because of the following informalities: Claim 29 is improperly dependent claim because it depends on itself. For examination, claim 29 has been interpreted to be dependent on claim 28. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-30 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transplanting a preparation of autologous pancreatic islet and endothelial cells, the method comprising administering said preparation to a non human mammal by injecting into hepatic portal vein such that it produces insulin for the treatment of diabetes, however it does not reasonably provide enablement for treating any patient by transplanting any insulin producing cells with any stem or bone marrow or genetically modified endothelial cells. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention recite an improved method for transplanting insulin-producing cells for the treatment of diabetes by manipulating the quantity and quality of endothelial cells in the transplanted material. Dependent claims list route of administration and type and source of insulin producing cells. Furthermore, subsequent claims describes endothelial cells are intra-islet endothelial cell, stem or bone marrow derived cells that further limits to genetically modified endothelial cells. It is noted that the intended use of these cells is for the treatment of diabetes by transplantation of these cells in a patient.

The application as filed is not enabling for the invention commensurate with the full scope of the claims because art of gene targeting and cell transplantation in human with stem or bone marrow or genetically modified endothelial cells for the treatment of diabetes was *unpredictable* as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, the broad aspects as well as limitations were not enabled for the claimed invention commensurate with the full scope of the claims at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention commensurate with the scope of the claim.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a

determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised by the art by artisan of expertise.

The specification as filed provides a general description of endothelial, insulin producing and other cell type and their growth conditions (pp 9-14). Page 9-17 describes genetic engineered endothelial and insulin producing cells. Page 17-25 provides a general description of vectors, tissue specific promoters. Page 26-39 of the specification discloses definition of terms, general description of biological method, method of gene delivery, transfection and a general description of different viral vectors. Rest of the specification teaches a general description of adjunct therapies, in vivo use

and devices for delivering the cell based therapies. In summary, the specification does not provide any specific guidance for the claimed invention commensurate with the scope of the claim because the specification as filed does not teach how to many endothelial cells are required, how to differentiate stem cells to endothelial stem cells or endothelial cells. Furthermore, It is noted that the specification does not provide any guidance as to how endothelial cells particularly stem or bone marrow derived cells would be genetically modified for the use in the host as cell therapy. The method of transplanting endothelial cell derived from stem or bone marrow in human was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

Specification's examples 1-2 on pages 48-56 disclose the expression of endothelial cell marker in isolated islet. This observation is followed by an experiment wherein inventor utilizes a model in which endothelial cells are tagged with Lac Z to show that lac Z expression recapitulate expression of Flk-1. Furthermore, inventor discloses in three different types of transplants that the islets are vasuclarized within the surrounding of islet graft. It also discloses that both donor and recipient endothelial cells are found within the islet graft area positive for insulin. These studies show that intra islet endothelial cells survive and contribute to revascularization process. Using the islet graft sections, it is further shown that the capillaries formed are either donor or recipient endothelial cells and chimeric blood vessels are formed from the mixture of donor and recipient endothelial cells. It also suggest revascularization of graft involves approximately 40% of the endothelial cells from the donor islet.

Although the specification show the role and importance of endothelial cells during successful islet transplantation, however these disclosures do not demonstrate the information required by the Artisan to reasonably predict the optimal number endothelial cells and insulin producing cells required for successful transplantation in the host mammal. The specification does not provide any specific guidance of any correlation between the number of insulin producing cells and endothelial cell that is required for the successful transplant. In other words, the art did not teach and was unpredictable at the time of invention, as to how many endothelial and insulin producing cells would be sufficient to produce insulin. In fact, even two years after filing this application Yechoor et al., (Gene Therapy, 2005: 12, 101–107) describes "ex vivo *gene* and *cell therapy* for diabetes in its nascent stage" (pp101, refer progress section) and predicts use of *ex vivo* gene therapy in combination with cell therapy only a realistic alternative to current islet transplantation protocols (Yechoor et al 2005; pp101, refer prospects) suggesting that cell therapy in human was unpredictable at the time of filing this application.

Given this lack of reasonable predictability in specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Specification does not provide disclosure on number of endothelial cell that are transplanted to elicit specific response. In absence of such guidance an artisan of the skill of the art would have to do undue experiment to determine the precise amount of

therapeutic composition needed to a patient. Although much will be dependent upon the specific requirement of the patient, however, without any specific guidance on how much insulin could be produced after transplanting preparations of islet and endothelial cell will not be enabling for the use in humans.

Next, claimed invention encompasses hepatocytes, neurons, myocytes or genetically modified cells as insulin producing cells. Transplantation of these cells in any patient and use of genetically modified non endocrine cells that could produce insulin was not routine at the time of filing of this application.

For example, Yamaoka, T., (Biochemical and Biophysical Research Communications 296 (2002) 1039–1043) evinces a positive outlook on non-β insulin producing cell but emphasizes ".... Although proliferation and apoptosis of β cells can be modulated by exogenous gene expression, an effective method for gene transfer into β cells *in vivo* has not as yet been developed".

Furthermore, the state of the prior art effectively summarized by the reference of Giannoukakis et al., (2002: BioDrugs 16(3) 149-173) state that more work is required to make hepatocytes or other non endocrine cells into fully surrogate β cells (pp163, paragraph 2). Giannoukakis et al states that gene and cell therapy strategies have been shown to be effective in preventing and treating type I diabetes in rodents and prolonging allograft survival in rodents and non human primate" (pp 167, paragraph 3). It is also noted that Giannoukakis et al., emphasize that safety issue should be addressed before starting any human trial. Pfeifer et al., (Annual Review of Genomics

and Human Genetics. 2001, 2: 177-211), describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Pfeifer et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed inventions resolution to vector targeting had not been achieved in the art and emphasized on development of more efficient and safe vectors (entire article, pp201).

In summary at the time of invention, the art of hepatocytes, neuron, myocytes or genetically engineered cells as insulin producing cell was unpredictable and the specification does not provide any specific guidance as to how these modified cells would have been transplanted in humans. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either.

Rafii et al., reviewed one year after filing of this application the state of the art of therapeutic stem cells and progenitor cell transplantation for organ vascularization and observed,

"Despite the contribution of bone marrow cells in tissue revascularization in animal models, the significance of these cells in restoring organ vascularization in clinical setting remains unknown (pp 703, 1st paragraph). Several recent clinical trials have challenged the potential of bone marrow-derived cells in restoring vasuclarization.... The success of these strategies depends on defining the mechanisms by which stem and progenitor cells undergo appropriate molecular education to direct their proliferation, mobilization and differentiation, thereby permitting

their functional incorporation into adult tissue." It is noted that contamination in preparations, factors that promote differentiation, route of delivery of stem cells may play a critical role in the outcome of tissue vascularization (pp 709, entire page).

It is noted, the specification is not enabling for practicing the claimed method of using any stem or bone marrow cells. The specification, does not disclose therapy guidance as to how would the method of ex vivo cell therapy would be carried out. For example, the specification does not provide any example or evidence as an artisan of skill would have been able to use stem or bone marrow cells for transplantation in human or number of cells that would be used for the therapy.

As shown above, the broad aspects as well as limitations were not enabled for the claimed invention at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. The application fails to provide enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method, (ii) the claimed method would have resulted in providing the increase number of endothelial cell in appropriate amount and quality during the transplantation of insulin producing cell for the treatment of diabetes. An artisan would have required to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of stem cell, gene therapy and cell transplantation *in vivo* was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. The specification and prior art do not teach a method of transplanting insulin-producing hepatocytes, neuron, myocytes or genetically engineered cell in humans. Furthermore, specification also fails to provide any guidance on *transplanting* endothelial cells, which are immortalized or derived from stem or bone marrow in humans. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and *in vivo/ex vivo* delivery and treatment of diabetes condition in general by cell therapy *in vivo* was unpredictable at the time of filling of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 4, 5, 8, 10, 21, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims 1, 4, 5, 21, 24 and 25 are vague and indefinite because they read on increasing the "quality" of endothelial cells. Since the term "quality" is not defined in the specification, it is not clear whether claimed invention is directed to a genetically modified endothelial cells or any other endothelial cells. Therefore the meets and bounds of the claim cannot be determined. Appropriate correction is required.

8. Claims 8 and 10 are vague and indefinite because they are drawn to a method of obtaining insulin-producing cell from "a distinct living donor". It is unclear what is meant by the "distinct living donor". Therefore meets and bounds of the claims cannot be determined. Appropriate correction is required. It is unclear what the "distinct living donor" means.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-4, 7-8, 10-12, 21-24, 26 rejected under 35 U.S.C. 102(e) as being anticipated by Revazova and Sebastian (US Patent Publication US2003/0113302A1 publication date 6/19/2003, filing date 8/30/2002).

Revazova et al teaches a method of transplanting tissue into a recipient to increase vascularization of the tissue by administering the endothelial cell and the tissue to the transplanted site (pp4; claim 1). The inventors also disclose that the tissue transplant is a pancreatic islet cells that is transplanted for the treatment of diabetes (pp 3; paragraph 30 and 31). Furthermore, the inventors also teaches combining tissue transplant with recipient endothelial cell either before or during transplantation and the transplantation method involves tissue contact with endothelial cell prior to transplant (pp 3; paragraph 33, 38 and 39). It is noted that optimization of endothelial cell quantity and quality, while propagating the cell culture is inherent in the teaching of Revaova et al. They also disclose use of immunosuppressive agents, growth factors and other substances with endothelial cells and/or transplant (pp4; paragraph 41). The invention also reads on to a method of treating humans with diabetes by transplanting autologus or allogenic islet and recipient endothelial cell (pp2 paragraph 22). In addition the inventor demonstrates the effectiveness of transplantation of islet cells and endothelial cells. The data in rodent model suggest that only the recipient endothelial cell could stimulate vessel formation in tissue transplant, whereas non-recipient endothelial cell had no effect on vascularization (example, paragraph 42-48).

Therefore, the claimed invention is anticipated by Revazova and Sebastian.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-4, 6-18, 21-24, 26-27 rejected under 35 U.S.C. 103(a) as being unpatentable over Revazova and Sebastian (US Patent Publication US2003/0113302A1, publication date 06/19/2003, filing date 08/30/2002); Osborne and Nagarajan (US Patent 6537806, dated 3/25/2003 filing date 11/4/1998); Kalka et al (Proc Natl Acad Sci U S A. 2000; 97(7): 3422-3427) and Ryan et al., (Diabetes 2002, 51(7): 2148-2157).

Revazova et al teaches a method of transplanting tissue into a recipient to increase vascularization of the tissue by administering the endothelial cell and the tissue to the transplanted site (pp4; claim 1). Revazova et al also discloses that the tissue transplant is a pancreatic islet cells that is transplanted for the treatment of diabetes (pp 3; paragraph 30 and 31). Furthermore, they also teach combining tissue transplant with recipient endothelial cell either before or during transplantation and the transplantation method involves tissue contact with endothelial cell prior to transplant (pp 3; paragraph 33, 38 and 39). It is noted that optimization of endothelial cell quantity and quality, while propagating the cell culture is inherent in the teaching of Revaova et al. They also disclose use of immunosuppressive agents, growth factors and other substances with endothelial cells and/or transplant (pp4; paragraph 41). The invention also reads on to a method of treating humans with diabetes by transplanting autologus or allogenic islet and recipient endothelial cell (pp2 paragraph 22). In addition the inventor demonstrates

the effectiveness of transplantation of islet cells and endothelial cells. The data in rodent model suggest that only the recipient endothelial cell could stimulate vessel formation in tissue transplant, whereas non-recipient endothelial cell had no effect on vascularization (example, paragraph 42-48). However, Revazova et al do not teach method of treating diabetes by transplanting cell preparation comprising genetically modified islet and endothelial cells from stem or bone marrow origin via injecting into hepatic portal vein of non-human mammal. Revazova et al also do not teach administering insulin or monitoring glucose and insulin levels in said non-human mammal.

Osborne et al teaches method of treating diabetes by transplanting into an individual genetically modified cell capable of cleaving proinsulin cleavage site and glucose regulated expressible nucleic acid encoding a protease capable of cleaving the proinsulin site to produce insulin (column 3, line 20-35 and claim 1). Osborne et al also describe different non-endocrine cells that can be modified to express insulin in glucose-regulated manner, which includes muscle (cardiac, smooth), fibroblast, liver, endothelial, epithelial and stem and germ cells (Column 24, line 30; abstract). Claim 7 and 26 recite insulin producing cells to be hepatocytes, neuron, myocytes or genetically modified cells. The cited reference has similar limitations.

However, Osborne et al do not teach transplanting genetically engineered cell capable of producing insulin along with endothelial cell that are either intra islet or derived from stem or bone marrow through hepatic portal vein. Furthermore, Osborne et al also do not teach insulin administration and monitoring of glucose and insulin levels in non-human mammal.

Claims 13-15 recite insulin administration, glucose and insulin monitoring in host. Ryan et al discusses a method of monitoring the glucose and insulin level in type 1 diabetic patients with islet transplantation (pp2149-2150, refer transplant procedure and metabolic monitoring). Figure 1B shows plasma glucose levels of standard meal tolerance tests in control subjects and patients before and after islet transplantation (pp 2151), while figure 3 teaches daily exogenous insulin use (U/kg) in relation to the number of islets transplanted (IE/kg) expressed for pre-transplant, after the first transplant and subsequent transplants (pp 2152). Ryan et al., also teaches hepatic portal vein as site of injection for islet graft implantation (pp 2149; transplant procedure). However Ryan et al do not teach islet graft implantation with endothelial cells.

Claims 16-18 are optimization and repetition of method that are inherent in teachings of Revazova and Sebastian as discusses earlier. An artisan of skill in art could further modify the steps taught by Revazova and Sebastian to obtain optimal outcome as stated in claim 16-18.

Kalka et al (2000) teaches transplantation of human endothelial progenitor cells (hEPCs) to athymic nude mice with hind limb ischemia. Kalka et al show blood flow recovery and capillary density in the ischemic hind limb is improved after hEPC administration. The authors emphasize that e*x vivo* expanded hEPCs may have utility in therapeutic neovascularization (abstract, figure 5). However, Kalka et al do not teach transplanting bone marrow derived endothelial cells for enhancement of angiogenesis along with insulin producing cell for the treatment of diabetes.

At the time of invention, it would be obvious to an artisan of skill to modify a method of treating diabetes of non-human mammal by genetically modifying muscle (cardiac, smooth), fibroblast, liver, endothelial, epithelial and stem and germ cells such that they produce insulin. Furthermore, state of the art teaches bone marrow or stem cells can be differentiated into endothelial cells for enhancing angiogenesis that could be transplanted by administering through portal vein along with insulin producing cell in a non human mammal for the treatment of diabetes with a reasonable expectation of success.

An artisan would have been motivated at the time of invention to genetically modify a non insulin-producing cell to produce insulin and use progenitor endothelial cell to enhance angiogenesis for the treatment of diabetes by transplanting them together via portal vein in a non-human mammal with a reasonable expectation of success because Osborne et al teaches different non-endocrine cells that could be modified to produce insulin. Ryan et al., teaches methods of administering cells and monitoring glucose and insulin levels in subjects. Kalka et al teaches use of progenitor endothelial cell and its contribution in angiogenesis during transplantation.

An artisan would have been motivated to combine the teaching of Osborne et al and Kalka et al in order to transplant insulin producing non-endocrine cells and progenitor endothelial cells into hepatic portal vein of a non-human mammal as described by Revazova and Sebastian (US Patent Publication US2003/0113302A1, publication date 06/19/2003, filing date 08/30/2002) for the treatment of diabetes.

Therefore, the claimed invention would have been prima fascia obvious to one of ordinary skill in the art at the time of the invention.

13. Claims 21, 28-30 rejected under 35 U.S.C. 103(a) as being unpatentable over Revazova and Sebastian (US Patent Publication US2003/0113302A1, filing date 08/30/2002) as applied to claims 1-4, 6-18, 21-24, 26-27 above, and in view of Rhim et al., (Carcinogenesis 19(4): 673-681); Takahashi et al., (In Vitro Cell Dev Biol. 1990 26(3 Pt 1): 265-74) and Bilbano et al., (US Patent number 6436393, dated 08/20/2002, filed on 4/29/1999).

Claims 29-30 recite transplantation of modified endothelial cell that is immortalized with a gene.

Revazova et al teaches a method of transplanting tissue into a recipient to increase vascularization of the tissue by administering the endothelial cell and the tissue to the transplanted site (pp4; claim 1). The inventors also disclose that the tissue transplant is a pancreatic islet cells that is transplanted for the treatment of diabetes (pp 3; paragraph 30 and 31). Furthermore, the inventors also teaches combining tissue transplant with recipient endothelial cell either before or during transplantation and the transplantation method involves tissue contact with endothelial cell prior to transplant (pp 3; paragraph 33, 38 and 39). It is noted that optimization of endothelial cell quantity and quality, while propagating the cell culture is inherent in the teaching of Revaova et al. They also disclose use of immunosuppressive agents, growth factors and other substances with endothelial cells and/or transplant (pp4; paragraph 41). The invention

also reads on to a method of treating humans with diabetes by transplanting autologus or allogenic islet and recipient endothelial cell (pp2 paragraph 22). In addition the inventor demonstrates the effectiveness of transplantation of islet cells and endothelial cells. The data in rodent model suggest that only the recipient endothelial cell could stimulate vessel formation in tissue transplant, whereas non-recipient endothelial cell had no effect on vascularization (example, paragraph 42-48). However, Revazova et al do not teach method of treating diabetes by transplanting cell preparation comprising insulin producing islet cell and modified endothelial cells.

Rhim et al., teaches immortalization of human umbilical vein endothelial cells (HUVECs) by human papilloma virus (HPV)-16 E6-E7 (abstract; Figure 2 and 7). It acquired an indefinite lifespan in culture without undergoing malignant conversion. However, Rhim et al do not teach combining these cells with insulin producing cells for transplantation.

Bilabano et al., describes gene transfer to human endothelial cells with an adenovirus vector encoding the $hbcl_2$ gene induced significant cytoprotection against apoptosis. It is also described that this cytoprotection might be useful in prolonging the survival of allograft (Column 23, paragraph 4). However Bilabano et al., do not teach combining these cells with insulin producing cells for transplantation.

Takahashi et al., have describes a cell line from the human umbilical vein and maintained for more than 5 year (180 generations; 900 population doublings) showing phenotypic alteration of normal human endothelial cells in vitro, and generation of a

transformant with indefinite life spans (abstract, figure 1). However Takahashi et al., do not teach combining these cells with insulin producing cells for transplantation.

At the time of invention, it would be obvious to an artisan of skill to modify a method of treating diabetes of non-human mammal by genetically modifying endothelial cells. It is disclosed in the art that lack of islet viability is one of the prime cause of islet transplantation failure thus use of immortalized endothelial cells to maintain vascular supply after islet transplantation in non human mammal would be an obvious goal of an artisan of skill in the art for the treatment of diabetes with a reasonable expectation of success.

An artisan would have been motivated at the time of invention to genetically modify endothelial cell to immortalize or promote growth for the treatment of diabetes by transplanting them together with an insulin producing cell in a non-human mammal because Rhim et al., teach immortalization of endothelial cells and Takahashi et al., describes a endothelial cell line maintained for more than 5 year and Bilabano et al., describe methods to reduce cell death in genetically modified endothelial cells . It would be obvious to one of ordinary skill to combine the teaching of either Rhim et al., or Takahashi et al or Bilbano et al to transplant genetically modified endothelial cells with insulin producing cells in a non-human mammal as described by Revazova and Sebastian (US Patent Publication US2003/0113302A1, publication date 06/19/2003, filing date 08/30/2002) for the treatment of diabetes.

Therefore, the claimed invention would have been prima fascia obvious to one of ordinary skill in the art at the time of the invention.

14. No Claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh, Ph.D.
Examiner, AU 1632